REMARKS

Applicants have amended claim 99. Applicants have added new claims 120 and 121. Support for these claims can be found throughout the specification as filed, and therefore no new matter is added.

35 U.S.C. § 112, Second Paragraph – Indefiniteness

The Examiner rejects claims 99-119 as being indefinite, stating that "said nucleosides" recited in claim 99 lacks antecedent basis. Applicants have amended claim 99 to delete "said" in front of the first occurrence of "nucleosides."

35 U.S.C. § 112, First Paragraph – New Matter

Claims 99-119 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement because they contain impermissible new matter. The Examiner states that there is no support for "about 1 to about 5 microns," or a "plurality" of 2'-O-methoxyethyl nucleosides as recited in claim 99. The Examiner states that there is no support for "at least about half" 2'-O-methoxyethyl nucleosides as recited in claims 108 and 118, or "about 15 to about 25 nucleotides in length," as recited in claim 109. Applicants respectfully traverse.

Applicants respectfully submit that the Examiner is applying an impermissibly strict "*in haec verba*" requirement. The proper test for satisfaction of the written description requirement is "[w]hether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1562-63, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991) (citations omitted). Applicants remind the Examiner that "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims," – conclusory statements are not sufficient. *M.P.E.P. §2163*. Only then does the Applicant need to respond to the Examiner's arguments.

Applicants submit that there is sufficient disclosure to support the phrase "about 1 to about 5 microns," as recited in claim 99. As the Examiner notes, Applicants disclose on page 62

that: "In order to reach the bronchiolar and alveolar regions of the lung, the particle size was targeted for 1 to 5 μm." *Specification* at 62 (emphasis added). One of skill in the art would understand that particles "targeted for 1 to 5 microns" encompass particles that are not precisely within the range of 1 to 5 microns – that is what "targeted for" means to those of skill in the art. Particles which are not exactly 1 to 5 microns are about 1 to about 5 microns. This disclosures clearly conveys to the skilled artisan that Applicants were in possession of and contemplated the recited range of "about 1 to about 5 microns." The Examiner bears the initial burden of explaining why this is not the case.

Applicants also submit that there is sufficient disclosure to support the phrase "wherein a plurality of nucleosides … are 2'-O-methoxyethyl nucleosides," as recited in claim 99, and "at least about half of said nucleosides … are 2'-O-methoxyethyl nucleosides," as recited in claims 108 and 118. A "plurality" refers to more than one, which Applicants have disclosed in the specification as filed. Similarly, Applicants have disclosed sufficient examples of oligonucleotides wherein at least about half of the nucleosides are 2'-O-methoxyethyl nucleosides. For example, on page 34, nine exemplary oligonucleotides are shown which have more than one 2'-O-methoxyethyl nucleoside, most of which are oligonucleotides wherein at least about half of the nucleosides are 2'-O-methoxyethyl nucleosides. The Examiner must explain why a person skilled in the art would not recognize in Applicants' disclosure an oligonucleotide wherein a plurality, or at least about half, of nucleosides are 2'-O-methoxyethyl nucleosides in view of this disclosure – verbatim support for "a plurality" or "at least about half" is not required.

Finally, Applicants also submit that there is sufficient disclosure to support the phrase "about 15 to about 25 nucleotides," as recited in claim 109. The Examiner acknowledges that Applicants expressly disclose "about 15 to 25 nucleotides" in the specification as filed. When "about" modifies a range, one of skill in the art would understand that both ends of the range are modified. Thus, "about 15 to 25 nucleotides" is simply a shorthand way of stating "about 15 nucleotides to about 25 nucleotides." The Examiner bears the burden of explaining why a person skilled in the art, typically someone with at least a Ph.D., would not recognize this from Applicants' disclosure – verbatim support is not required.

Applicants submit that the Examiner has not met her burden of establishing that the rejected limitations are not supported by Applicants' disclosure, and that for at least the above reasons, Applicants' disclosure and priority documents provide adequate support for the recited claim limitations. Applicants therefore request that the Examiner reconsider and withdraw the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, as containing new matter.

35 U.S.C. § 103(a) – Obviousness

Claims 99-119 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyce *et al.*, (WO 96/40266) in view of Nicklin *et al.* (WO 98/09633) and Levesque *et al.*, (Mol. Pharmacol., 51, 1997, 209-216). *Office Action* at 6. The Examiner asserts that Nyce discloses the invention with the exception of 2'-O-methoxyethyl and 5-methylcytosine modifications, and that the oligonucleotides of Nyce are not 20 nucleotides in length. *See Office Action* at 7. The Examiner asserts that Nicklin and Levesque disclose the missing elements, that it would have been obvious to modify the antisense of Nyce to include the modifications of Nicklin and Levesque, and that the level/degree of modification amounts to routine optimization. Applicants respectfully traverse.

First, Applicants submit that the Examiner is improperly using hindsight to restrict the number of possible variables that would have to be modified/optimized to arrive at the claimed invention. *See M.P.E.P. §2142* (The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.)

Starting with the disclosure of Nyce, the Examiner must articulate a reason one of skill in the art would modify the oligonucleotide of Nyce to arrive at the claimed invention. The Examiner states that "[o]ne would have been motivated to incorporate 2'-O-methoxyethyl or 5-methylcytosine modifications into the oligonucleotides of the method of Nyce et al. because Nicklin teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target." *Office Action* at 8.

This statement ignores that fact that Nicklin does not limit the modifications which provide these improved characteristics to only 2'-O-methoxyethyl or 5-methylcytosine

modifications. Instead, Nicklin discloses literally hundreds of preferred modifications which one of skill in the art would have to consider if one were to look to modify the oligonucleotide of Nyce. *See Nicklin* at 2-5. Thus, if one of skill in the art were motivated to begin modifying and optimizing the oligonucleotide of Nyce in view of Nicklin, there would be literally millions of combinations to consider for optimization, not just the two modifications identified by the Examiner based on Applicants' disclosure.

Second, the obviousness of modification and optimization must be evaluated according to the teachings of the prior art, including teachings away from the claimed subject matter:

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). *M.P.E.P. §2141.02 VI* (emphasis in original).
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> A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). *M.P.E.P. §2144.05 III.*

If one of skill in the art were to modify/optimize the oligonucleotide of Nyce, the previously cited Yu reference would be particularly relevant because it was designed to test the effects of different modifications of oligonucleotides. However, as stated previously, the Yu reference teaches away from modifying Nyce to incorporate a plurality of 2'-O-methoxyethyl nucleosides in the oligonucleotide as recited in claim 99.

Molecules 1-6 of Yu were tested for their ability to inhibit HIV-1, with molecules 2-4 differing in the number of 2'-modified phosphodiester nucleosides included. Table 2 demonstrates that molecule 4, which had the most 2'-modified nucleosides, had the worst activity, while molecule 2, which had the fewest 2'-modified nucleosides, had the best activity of molecules 2-4. While molecules 2-4 also had different amounts of phosphodiester internucleoside linkages, molecules 1 and 6 differ only in the number of 2'-modified nucleosides. Importantly, the molecule with the best activity reported in Table 2 contains zero 2'-modified nucleosides, although it is only slightly better than molecule 6, which contains several 2'-modified nucleosides. Thus, Table 2 of Yu would not lead one of skill in the art to modify the molecule of Nyce *et al.* to include a plurality of 2'-modified nucleosides, since Table 2 suggests

that the more 2'-modified nucleosides that are included, the worse the molecule performs, and having no 2'-modified nucleosides is best.

Newly cited Levesque does not offer any additional disclosure to counter the teachings of Yu that fewer 2'-modifications are better. Levesque does not contain any direct comparisons between modified and unmodified oligos. Finally, Applicants note that Nicklin discloses that one of the "especially preferred embodiments" is one which contains no 2'-modified nucleotides. *Nicklin* at 4. Thus, considering Yu, Nicklin and Levesque in their entirety, one of skill in the art would not be led to the claimed invention, but rather would likely conclude that fewer 2'-modified nucleotides are better.

Applicants note that the Examiner does not address the teachings of Yu in the latest Office Action, stating only that "the Yu et al. reference in the rejection under 35 U.S.C. 103(a) was relied upon for teaching gapmer configurations, which are not an element of the newly added claims." *Office Action* at 2. Applicants respectfully submit that the Examiner cannot ignore the teachings of Yu because the claims no longer expressly recite gapmer configurations. The Yu reference is of record, and the Examiner must evaluate obviousness in view of the entire record, not just those references which support the Examiner's position. *See M.P.E.P. §2142* ("The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992).") (emphasis added).

Finally, even if the Examiner has established a *prima facie* case of obviousness, a point which Applicants do not concede, Applicants submit that the claimed method provides unexpected results. "The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983) that 'evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness.'" *M.P.E.P. §716.01(a)* (emphasis added).

Contrary to the teachings of Yu *et al.*, Applicants have found that incorporating more 2'-modified nucleotides improves the uptake of oligonucleotides, which will result in improved activity for the same amount of oligonucleotide. Example 3 of the instant application discloses the results of *in vivo* administration of aerosolized nucleotides into the lung. Tables 2 and 3 shows the concentration of oligonucleotide in the lungs of mice following single and multiple

administrations, respectively, of three antisense molecules. Importantly, ISIS 15163 performs as much as 4 times better than ISIS 17009, even though the only difference between the two molecules is the fact that ISIS 17009 does not contain any 2'-modified nucleosides, while ISIS 15163 does. Because uptake of the molecule is directly related to its activity, this is clearly unexpected in view of Yu *et al.*, which shows that the inclusion of 2'-modified nucleosides at best has no effect, and at worst decreases the activity of the molecule.

For at least the above reasons, Applicants submit that the pending claims are patentable over Nyce, in view of Nicklin, and Levesque. Applicants therefore request withdrawal of the rejection of the pending claims under 35 U.S.C. § 103(a).

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Examiner's attention to the following patents or applications. Applicants encourage the Examiner to review and monitor the prosecution of the following patents and/or applications throughout the pendency of this application.

Patent / Serial Number	**Title**	**Issued / Filed**
09/083,586	COMPOSITIONS AND METHODS FOR THE PULMONARY DELIVERY OF NUCLEIC ACIDS	5/21/1998

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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By: _____

Brenden S. Gingrich
Registration No. 60,295
Attorney of Record
Customer No. 55,389
(619) 235-8550

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